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NATIONAL INSTITUTES OF HEALTH IN THE TROPICS*

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INTRODUCTION BY DR. GUERRANT

It is certainly an extraordinary privilege and a great honor for me to introduce our very distinguished Charles Franklin Craig Lecturer this year. Named for one of our Society's founders and the editor of our Journal for 20 formative years from 1927 to 1947, the Charles Franklin Craig lecture is a traditional highlight of our program. Thanks to our archivist, Don Burke, we actually have here Colonel Craig's original sword, now offered symbolically for the cutting of red tape and for leadership in the attack on tropical diseases, leadership that is clearly being forged by our distinguished Craig lecturer this year, Dr. Harold Varmus.

Dr. Varmus grew up in Long Island, New York the son of a family physician and social worker. His bachelors and masters degrees from Amherst and Harvard are in English literature. After medical school and medical residency at Columbia University and Columbia Presbyterian Hospital and two years at NIH, he then joined Dr. Michael Bishop at the University of California at San Francisco to study tumor viruses. It was there as Professor of Microbiology, Biochemistry, and Biophysics and as the American Cancer Society Professor of Molecular Virology that he and Bishop showed that cancer genes (oncogenes) can arise from normal cellular genes, work for which they shared the 1989 Nobel Prize in Physiology or Medicine. Dr. Varmus is beginning his fifth year as Director of the National Institutes of Health.

Author of some 300 scientific papers, a member of IOM, the National Academy of Sciences, and the American Academy of Arts and Sciences, his most recent of four books is for a general audience entitled *Genes and the Biology of Cancer*.

But perhaps most poignant to this audience in this Stellar career, Dr. Varmus worked as a medical student for three months in a mission hospital in north India, work that clearly influenced his profound commencement address at his alma mater, Columbia College of Physicians and Surgeons earlier this year. Ladies and gentlemen I present to you Dr. Harold Varmus, who will speak on NIH in the tropics.

Dr. Varmus:

Well, Dick thank you very much for the sword. As I do a lot of cutting of red tape, this will be quite useful. I am very pleased to have a chance to speak in memory of Colonel Craig, whose 1909 book on malarial fevers had a very strong influence on the field I will talk about a bit. There is indeed some irony in my giving this lecture today. Because at one time, perhaps 30 or so years ago, I might have viewed the prospect of giving this lecture as a high point in a career in tropical disease. I went to medical school with an interest in psychiatry but quite quickly deviated from that focus and, under the influence of a number of factors, became interested in tropical disease. First I was influenced by tales of adventure and exciting medical science in the classroom of Harold Brown—so called stooly Brown—perhaps known to many of you. I then became an International Fellow at Columbia University as a medical student and indeed wrote a paper about social and economic consequences of reducing childhood death rates in poor countries.

Then in my fourth year in medical school, as Dick mentioned, I received a fellowship from a drug company to work in a mission hospital in north India. This was a valuable and fascinating experience. It was also sobering and, perhaps unfortunately, once again course altering. I recently found, as a result of my wife's insistence that we unpack the boxes we brought from California four years ago, a 20-page report that I had written in 1966 describing my several months in that north India mission hospital. In the report, I encountered my harsh criticism of the medical, social, and fiscal practices in the hospital in which I worked: the unfortunate billing practices; the reluctance to supply transfusions until patients had put up their money; the abysmal conditions in which patients lived; the failure of the hospital refrigerator that housed blood, which was not detected until several patients had died of septicemia. These case reports were mixed with another case report of a medical student fellow—namely, myself—who was suffering from amebiasis and scabies. I also found fixed to that report a letter from the Director of the Division of International Medical Education of the American Association of Medical Colleges, saying he found my report "particularly informative" but adding that he presumed that I had no plan to publish the report. Its publication, he said, would not be constructive. So this experience, with many facets of suppression and degradation of some of the patients I watched, and the simultaneous lure of academic medicine and later research in molecular biology and virology moved me into a very different career track—one that would not normally lead to an opportunity to give this Craig lecture.

So it is with some trepidation that I deliver this lecture, with its implied claim to knowledge about tropical diseases, to an audience that is much more devoted to the diseases, schooled in the sciences, and traveled in the tropics. Nevertheless, it has come to pass that in my not-so-new job as Director of NIH, I have become very familiar with many aspects of one important tropical disease, namely, malaria. This happened because of a somewhat innocent proposal that I made at the end of a workshop organized by the Fogarty International Center in July 1995. This workshop was set up with my approval to explore ways to enhance science and health in Africa. This was being done in part because of concern by many of us in leadership roles at NIH that most of Africa was being left increasingly far behind, behind even Latin America and poorer parts of Asia, with respect to technical development, scientific infrastructure, and health.

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In the one day of that conference we listened to descriptions of many health problems and scientific opportunities in Africa on a very wide range of topics: the genetics of many diseases, iron metabolism diseases, hypertension, many aspects of diabetes in Africa, and a wide range of infectious illnesses. We learned about multiple ways in which various nations and research and development agencies were independently attempting, usually one to one (one agency or one country to one site in Africa), to nurture science in many different countries in Africa. This discussion made many of us feel that it might be useful to test the merits of a more coordinated attack. We proposed to do that by focusing on a single important disease and trying to mount a joint multinational effort to combat that chosen illness with the full participation of our African colleagues.

It seemed to me and to others at that meeting that malaria might be a particularly appropriate focus. Indeed, it is a very big problem, with roughly 300–500 million people infected on the surface of the earth; roughly 1–2 million deaths, 90% of those in Africa, each year. And yet only 85 or so million dollars being spent world wide on malaria research. It was also an attractive target because there were many points of attack on this problem: prevention through insect control and bed nets, many forms of treatment available, approaches at the biological level to parasite and mosquito and even to the human host, and evidence of an immune response that had not yet been harnessed to produce a vaccine. Many aspects of health services, such as control and education, were intimately linked to the biology of the disorder and its transmission. There was also considerable research experience in many countries in Africa, with many funding agencies doing various things to try to foster research on malaria. There was, happily, a significant cohort of African scientists. Many of them were now working in their home countries, usually after being trained in the northern countries. And there was clearly a need to do the science in Africa because the study of the epidemiology and pathogenesis, clinical trials of either preventive or therapeutic maneuvers, and the study of health services and case management clearly had to be carried out where the disease was actually occurring. This need also allowed us to stress a companion need to maintain both practical approaches and more theoretical scientific approaches moving in a hand-to-hand fashion. That is, for example, to study the efficacy of bed nets together with the nature of the insecticide in which they are impregnated; to study water control side-by-side with the epidemiology of the disease. The distribution of mosquito vectors, insect reduction, provision of common treatment, education programs—all these things need to go hand-in-hand with a scientific appreciation of the disease. Furthermore, there remained an appreciable scientific interest in northern countries in the problems that malaria poses, while there is also a clear appreciation of the potential that recent scientific advances present in addressing malaria as a research problem. In addition, there is an alleged loss of support from pharmaceutical companies for malaria research. Nevertheless, a focus on malaria raised the prospect of substantial local political support for any initiative we might undertake.

So malaria was clearly a good choice. But one had to ask, with many kinds of activities already under way and many other possible targets for such initiatives, why would this be a propitious time to undertake an expanded effort specifically on malaria? There are at least three reasons that seemed powerful to me. First is the evidence of the strong resurgence of malaria, a resurgence that can be attributed to a number of factors—in some cases, simply the failure of will to maintain control programs; but also, perhaps more profoundly, the gradual increase in resistance of insects to insecticides and of parasites to drugs. Chloroquine-resistant organisms have arisen independently in at least two places, Southeast Asia and northern South America, and spread throughout much of the tropical world. (Sue and Wellems and their colleagues recently published a paper on a gene candidate for chloroquine resistance in *Plasmodium falciparum*.)

The resurgence of malaria is well documented, even in my own life. When I look back at my 1966 report from India, what I read is, "although malaria has been largely eradicated by the efforts of WHO, other infectious problems remain in abundance, particularly tetanus, cholera, ameba, and round worms." Some years later, in 1988, I returned to India for teaching purposes, and I did not have long to wait to see how the fortunes of malaria had changed in 22 years. Soon after getting off the plane, I picked up a newspaper that had on its front page stories of a wide spread epidemic in Bujurat, with many thousands of individuals dead of *P. falciparum*. Any of us can see clearly from our travel that this resurgence is very strong.

The second reason I believe expanded efforts are especially appropriate at this time is that the very strong scientific infrastructure and the availability of new techniques are going to have a profound effect on our approach to malaria. There are genome projects under way on *P. falciparum* itself and *Anopheles gambiae*, the major African vector. There are advances in cell and developmental biology that are profoundly altering our understanding of the parasite and its vector. We do not have to think very hard, especially in this group, to envision how such information could be applied to the design of new vaccines by choosing more appropriate immunologic tools with better antigens, by understanding the immune system and its response to the malarial parasite, by defining better targets for new drugs such as proteases and others. It has become apparent from recent experiments that by understanding the life cycle or the parasite more profoundly that gene targeting approaches may have the potential to detect and alter genes that might not have been suspected as being essential for the development of the parasite in the mosquito. New understanding of adhesion of the parasite to red blood cells and the role of this process in the pathogenesis of malaria is also promising. For example, by identifying the cell surface proteins encoded by the parasite that are involved on the surface of red blood cells, we raise the possibility of designing drugs that might interfere with those interactions and thereby open new possibilities for preventing and treating cerebral malaria in children or improving the fate of pregnant women with malaria.

The third reason for believing that this is a good time to expand our efforts, especially efforts carried out in Africa, is the rapid advance in our means to communicate in Africa. It is now possible, in principle if not in practice, to be an up-to-date scientist anywhere, even in Africa. E-mail, pubmed, the Internet, and computer links to databases and to colleagues are advances that profoundly change the prospect

for doing science in parts of the world that were previously incommunicado.

So these workshops and discussions have led to what is now called the malaria initiative or the Multilateral Initiative on Malaria (MIM). I want to review with you some aspects of this initiative to give you some sense of how this kind of thing develops. Remember our workshop was held in July 1995. Over the next several months additional meetings were held to try to plan a major gathering of the malaria research community and its funders.

Over the course of 1997, three major meetings were held: in Dakar, in the Hague, and in London. These three meetings seen in order describe a kind of Hegelian rhythm with a thesis, antithesis, and syntheses. The first meeting in Dakar was a distinct upper. Many in the malaria community now talk about "the spirit of Dakar" because the meeting was simply extraordinary in my own experience and in the experience of most who were there. First, among the 150 participants were very many African scientists, most of whom were working in their home countries. Roughly one-third of the scientists at the meeting were Africans working in Africa. Many of these scientists were meeting their colleagues for the first time because, as many of you know better than I, traveling from East to West Africa can be rather difficult. The African scientists shared a role completely equal to that of the sponsors and scientists from Europe and America, and that too was unusual.

Second, the meeting was unusual because of its format, which was entirely communal. We divided up into nine or so special topic groups, and the purpose of these groupings was not to allow the three or four most prestigious scientists to present their hottest results but, instead, to allow the entire group to think together about the goals of their common interests—whether it was case management, entomology, immune response, or pathogenesis—and to ask what had been achieved, what should be achieved over the next 5 or 10 years, and what were the obstacles to achieving those goals. Some very interesting themes emerged that, in fact, cut across all the groups: the variability of malaria from site to site, the difficulty people were having comparing results at different sites because of the use of different methodologies and different reagents, the need for a reagent inventory so that people could use standard strains and standard mosquitoes, and a very common need for improved communications among African scientists and between African scientists and those in Europe and America.

A third issue that was palpable to me was a very strong link between the theoretical and the practical, between the basic and the applied. Considerations of the epidemiology of the disease were closely linked to efforts to understand the genetic bases of drug resistance and to the development of drugs that would be effective in those regions where there has been high penetration of drug-resistant strains.

Another aspect of the meeting that was unusual in my experience as a fairly veteran meeting goer was the very strong political support from African leaders. For example, at the opening of the meeting, we received President Diofe of Senegal and many other leaders who turned up to officiate. I am not a lover of ceremonies, as many of those who know me will appreciate. Nevertheless, the strong political buy-in that comes from having the President of the host country come and display not just an interest in the formalities of the meeting but an actual understanding of the impact of malaria on his own country sent a profound message and a very strong sense of the importance of the meeting to those who were there. At the end of the meeting, it was decided to form this Multilateral Initiative on Malaria, or MIM, and to call for some letters of interest from scientists who wanted to work together to develop collaborative arrangements, particularly so-called research networks in which methods and materials would be shared and better forms of communication would be developed.

The next gathering of the clan, at the Hague in July, was billed as an effort to evaluate those letters of intent for forming those collaborations. Instead it became the antithesis in our Hegelian formulation, the point in the growth of MIM at which reality was encountered. At this second meeting, it was appreciated more profoundly than before that funds were quite limited. It became apparent as the funders began to discuss the mechanism or mechanisms by which proposals would be supported that there were competing bureaucracies, with no clear consensus on methodology that could be used for funding these proposals. Many saw a need to create broader interfaces with government and industry and to create a much more extensive role for advocacy for malaria research, as opposed to doing a few small things that had primarily symbolic value.

After that meeting, in which there seemed to be some realignment of interests in the proceedings and some slowing down of progress toward the common goal, there was a third meeting, in London just last month, hosted by the Wellcome Trust. This meeting seemed characterized by a much more harmonious assignment of tasks. The task became more diverse than perhaps had been originally intended, but it seems clear now that the Wellcome Trust is going to act as a secretariat for this activity. The Malaria Foundation will be acting as the chief advocate for malaria research. The WHO, TDR, headed by Tore Godal, has established a small pot of common funds—provided by the NIH, World Bank, TDR itself, WHO Africa, and we hope a few additional organizations—and they will be funding some of the proposals when they are submitted in a more refined form. Those proposals are intended to emphasize collaborative research networks and resource building. It is still a small amount of money, but we think it can do a great deal to improve the infrastructure in which malarial scientists work, especially in Africa.

In addition, the National Library of Medicine—a component of the NIH—has been making real progress, one country at a time, in developing a stronger informational infrastructure and a better communications network. NIH computer scientists have gone to Mali and helped at the NIH-supported center there, and they are now going to Kenya, Tanzania, and one still-unselected Francophone country to try to build more secure Internet communication and hardware and software in those countries. This means not just supplying the materials and moving on but actually helping to train individuals to handle problems on the ground as they occur after our scientists leave. The National Institute of Allergy and Infectious Diseases (NIAID) at the NIH has also been hard at work trying to build databases, a repository, and common research protocols. They have recently held a

workshop on this topic, which is one of the tasks we agreed to at the meeting at the Hague.

Now I want to go beyond malaria for a few minutes and think about the significance of these developments in the context of efforts that might be undertaken for other diseases, because you might legitimately ask whether the NIH is interested only in malaria or has interests in other diseases that affect the developing world. You have heard from your President that a fairly small fraction of the total NIH budget is distributed in such areas. I want to give you a little more feel for what really goes on. We have about two hundred million dollars in our budget that is identifiably international. That is, it is devoted to the training of foreign nationals that come here, to training programs that we support abroad, and to our own citizens who go to other countries for training. It also includes awards for research projects and awards for collaborative research that involves foreign components. The NIH also spends a great deal of money on diseases that are uniquely tropical or seen abroad but are studied only in this country. These would not be counted inherently as international expenses, but they involve many of the grants awarded to many of the people in this room for studies carried out in the United States that clearly involve diseases that are unique or nearly unique to other parts of the world. In general, our work on such diseases, particularly tropical illnesses of the sort studied by members of your Society, has been increasing. For many of the major disease areas that you are concerned with here, such as filariasis and malaria research and research on vectors and tropical viruses, NIH spending has been increasing quite dramatically. And in general the amount of money we are spending in tropical diseases has been rising, particularly in the one institute, NIAID, that does support most of the NIH work in these areas.

I will make another point as a kind of advertisement about NIH's involvement in international health. We are currently seeking through our conventional recruitment process an Associate Director for International Health who would be working within the Office of the Director—my office—meeting with my own staff and serving concomitantly as the Director of the Fogarty International Center. This recruitment implements a recommendation that comes from a recent report by Barry Bloom and Josh Lederberg, who reviewed the international research activities at the NIH for me about two years ago. So if you have friends, candidates, worthy folk you think would be suitable for this position, please recommend them to us so the search committee is aware of candidates that we might not otherwise know about.

I would also like to make a point about the interest of the NIH in international health that has to do with the kinds of arguments we believe we should be making as a federal agency for funding and political support in these areas. Your President has reviewed many of these and I definitely agree with him. In fact, I was quite touched by the poem, "Unthinkable Entrapment," because I have recently reread an article about malaria that appeared in the *New York Times* last January, in which the reporter describes a woman with five or six children and one bed net trying to decide each night whether to put the two-week-old child who probably won't survive or an older child in the bed net. The kinds of rationales that my own thinking leads me to espouse in government councils or in places like this are very similar to the list you heard about from your President. First, the humanitarian approach, that is, this is the right thing to do. Second, the economical approach, that is, there is a real virtue to developing stronger countries that buy the commercial products that create better health and better markets. And third, there is an American foreign policy interest in political stability that seems to me quite powerful.

My favorite article on this topic was one by Jeffrey Goldberg, published in the *New York Times Magazine* on March 2, 1997. I recommend to those of you who have not seen it that you get hold of this article, whose point is summarized in the following quotations: that "biological stability flows from political stability," that "chaos . . . is the best incubator of disease," and that "disease is also an excellent incubator of chaos. It is an endless cycle of misery." The notion of coupling the political stability of a country to its health and well-being is a particularly profound insight—perhaps an obvious insight to many of you who have been to those countries, but to the average person in our country who is unaware of the way in which these two components are closely linked in countries of Africa and other parts of the developing world. This is an important idea. This was brought home most powerfully to me by a trip I took to Mali after the Dakar meeting. I could see the effect of the strong collaboration between the NIH and the Malaria Research and Training Center at the University of Bamako—the effect on the University, on the town, and on the entire government. The President of Mali, Dr. Kanary, himself an archeologist, is intimately acquainted with the personnel and the activities of the Center. He is proud of the Center. It is a strong point in his effort to democratize Mali. Those research efforts, which are often conducted in the villages, can have profound effects on health. In the town of Makainono, at which the Malaria Center has an active program, not only have the townspeople who are actively involved in the research project learned about malaria and how it is transmitted, but they have also improved their local health and health resources for many other diseases. A good well has been built, and the incidence of infantile diarrhea has diminished markedly. This kind of effect can obviously be transmitted to many other places.

I would like to conclude with a few general observations of things that I have learned from my intermittent but active involvement in the problem of malaria in the last couple of years. First, health issues in the tropics are becoming more like health issues elsewhere. Despite the need to focus on diseases like malaria, we have all learned from the book that your President cited many times, *The Global Burden of Disease*, by Murray and Lopez, that for the aging of the population and the partial control of infectious diseases, we are beginning to estimate that by 2020 the difference between the developing world and the industrialized world will become less. We need to take that into consideration as we continue our efforts in the classically tropical diseases.

Second, we need to remember that there are those diseases that are nearly unique to the tropics, with only some modest penetration into the more developed countries, and then there is a whole class of diseases—tuberculosis, HIV, and certain other viruses among them—that are very common in both cultures. It is important to remember as we think about the

impact of NIH-supported research on the third world that many of the things we do and we consider uniquely NIH efforts, like our work on HIV, has a major impact in the developing world as well.

It has become apparent to me that there is an increasing potential for basic science, perhaps of the type now possible only in the most developed countries, to enable more rational approaches to those things most desperately needed in the developing countries—namely, simple therapies and more effective vaccines. This may be true of a much wider range of diseases than simply malaria. It is a phenomenon that I believe is also affecting our thinking about cancer and heart disease and many other diseases that we encounter in all parts of the world.

I have been struck with the power of interdisciplinary messages, if you will, the effect of learning about one thing on our attempts to understand something else. That has certainly been profoundly true in my own field, cancer, in which our efforts to understand how cancer genes work has had a tremendous impact on our thinking about many other diseases in which it is important to understand how a signal is transmitted from the surface of a cell to the interior of a cell. Our thinking about cardiovascular and metabolic disease has been profoundly affected by the availability of certain genes we know to be involved in the causation of cancer. Similarly, our efforts to understand the immune response in malaria is going to have important implications for two other major diseases caused by very different kinds of infectious agents, namely, HIV and the tubercle bacillus, which also establish chronic infections to which there is an immune response which is incomplete and for which there are no vaccines currently available.

Another point that occurs to me as I think about the impact of new basic science and new methodologies on our attempts to solve disease problems is that although many of these new tools are generated only in the developed countries, they can be transferred into research projects in countries like those of Africa without the great difficulty one might have supposed. For example, the use of simplified genetic analysis tools like array chips and other kinds of devices, PCR, may have a great effect on our understanding of the epidemiology of malaria, case management, and following drug resistance. These tools may indeed be the solutions to the long-standing problems of how to do genetic analyses of organisms and vectors under conditions where elaborate and complex manipulations have proven difficult. Another observation that has become quite clear to me is that there is now an increasingly robust cohort of well-trained scientists native to many of the countries that for political and economic reasons often do not foster the research environment necessary to do some of the science so urgently needed. It is important for us to be developing the interactive tools to maintain strong collaborations with these scientists, but in a way that maintains these scientists as equals in the partnership and that gives them credibility in their home country so that their political framework is as supportive of them as we would like our fellow scientists to be. Finally, if we are going to expand our activities, we need to stress the importance of thinking about many disciplines at once, not just the science but also the economics, the politics, and the health services components of what our research conveys.

I know that over the last 20 or 30 years, since I was a medical student, tropical medicine research has moved quite far into the mainstream at medical schools and academic health centers. This has happened in a way that has been effective in trying to draw the attentions of geneticists, cell biologists, and computer scientists to the problems that your members are most concerned about. This is a very important factor in the changing environment at such institutions and I very strongly believe that departments of cell biology and genetics should have people that are working on these problems. Nevertheless, it is the core of the tropical disease scientific community, the core represented by this Society, that will continue to be central to the developments that I and others would like to see occur in our efforts to combat diseases of the tropical world. I am very pleased that we have had such enthusiastic support for the malaria initiative from your members and look forward to many other productive projects in the future. Thank you very much.

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Dr. Guerrant:

Dr. Varmus, I know that I speak for all of us in thanking you tremendously for the support, your vision, and all that you are doing for our field, your field, our field together of Tropical Medicine. In appreciation, the Society presents you this plaque stating that "*The American Society of Tropical Medicine* presents to Dr. Harold E. Varmus this certificate of recognition and appreciation for your efforts as Director of the U.S. National Institutes of Health to increase recognition of the severity of malaria as a global health problem, to stimulate collaborative research and training, and to develop and improve tools for malaria control." We are very grateful to you for this pioneering effort.